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UNITED STATES DEPARTMENT OF COMMERCE
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Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/124,485	07/29/98	ANSTEY	N 73-97

HM22/0703
GREENLEE WINNER AND SULLIVAN
5370 MANHATTAN CIRCLE
SUITE 201
BOULDER CO 80303

EXAMINER	
GABEL, G	
ART UNIT	**PAPER NUMBER**
1641	9

DATE MAILED: 07/03/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/124,485	Anstey et al.
Examiner	**Group Art Unit**
Gallene R. Gabel	1641

☒ Responsive to communication(s) filed on *Mar 24, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-26* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-26* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Restriction/Election

1. Applicants' election of Group I, claims 1-26, with traverse, on 3/24/00 in Paper No. 8 is acknowledged and has been entered. Claims 27-33 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Priority

2. This application filed under former 37 CFR 1.60 lacks the necessary reference to the prior application. A statement reading "This is a continuation of Provisional Application No. 60/054,114, filed 7/29/97" should be entered following the title of the invention or as the first sentence of the specification.

Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CAR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not state whether the inventor is a sole or joint inventor of the invention claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 3-17, 19-21, 24-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in reciting "nitric oxide modifying agent" because it is unclear as claimed, what is encompassed by the term "modifying", i.e. do applicants intend to encompass change in level, effect, phase, structure, etc. See also claims 2-3, 10, 13, 16-19, 22-24.

In claim 1, replace "an" with --a-- to correct typographic error.

Claim 3, (iii) is vague and indefinite in reciting the term "associate" because it is unclear as to what is encompassed by the term "associate" as used in the claim.

Claims 4-16 have improper antecedent basis problems in reciting "A method according to claim ...". Change to --The method according to claim...-- for proper antecedent basis. See also claims 20-21 and 25-26.

Claim 11 recites improper Markush language in reciting "wherein the organ or tissue targeted is selected from". Change to --wherein the organ or tissue targeted is selected from the group consisting of-- for proper Markush language.

Regarding claim 13, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). See also claim 15, first and second occurrences, 19(iii), 24, first and second occurrences.

Regarding claim 14, the phrase "a chemical derivative thereof" renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "a chemical derivative thereof"), thereby rendering the scope of the claim unascertainable. See MPEP § 2173.05(d).

Regarding claim 15, the term "includes" renders the claim indefinite because it is unclear whether the limitation following the term are part of the claimed invention. See MPEP § 2173.05(d).

Regarding claim 15, "e.g." renders the claim indefinite because it is unclear whether the limitation following "e.g." are part of the claimed invention. See MPEP § 2173.05(d).

Claim 15 is indefinite in using parenthetical symbols because it is unclear whether the limitation within the parenthesis is part of the claimed invention. See MPEP § 2173.05(d).

Claim 16 is confusing in reciting "the agent comprises a combination of one of a nitrosothiol and the other an agent selected from a cytokine and a chemotherapeutic agent" because it is unclear as to whether the agent comprises "a combination ... of a nitrosothiol and ... an other agent" or whether the "an other agent selected from" is a separate agent for the same purpose. Please clarify.

In claim 17, change "administered" to --administering-- to correct typographic error.

Claim 19, (iii) is vague and indefinite in reciting the term "associate" because it is unclear as to what is encompassed by the term "associate" as used in the claim.

Claim 24, (iii) is vague and indefinite in reciting the term "associate" because it is unclear as to what is encompassed by the term "associate" as used in the claim.

Regarding claim 19 (iii), the phrase "their equivalents" renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "their equivalents"), thereby rendering the scope of the claim unascertainable. See MPEP § 2173.05(d).

Regarding claim 24 (iii), the phrase "their equivalents" renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "their equivalents"), thereby rendering the scope of the claim unascertainable. See MPEP § 2173.05(d).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for **a method of treatment of infection** in animals **by intracellular protozoan parasites** such as Plasmodium species (encompassing those that cause malaria), does not reasonably provide enablement for a **method of prophylaxis** of **uninfected animals by parasitic intracellular or extracellular protozoans,** including the Plasmodium species. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

As set forth in *In re Wands,* 858 F .2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of the experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of prior art, the relative skill of those in the art, and the breadth of the claims.

As to the method involved, the direction and guidance in the specification is notably limited to *specifically* treating diseased patients with existing malaria infection, such as administering safe amounts of NO and NO "modifying" agents to inhibit certain life cycle stages, retard growth, or annihilate existing parasites that cause malarial infection in patients. The working examples and disclosed uses are limited to inhibiting parasitic proliferation and ameliorating clinical symptoms in diseased patients, etc. Based on this limited disclosure and direction, one of the skill in the art would not know how to provide alternative treatment methods for preventing malarial infection to a non-infected human/animal, such as the claimed prophylaxis (vaccine) treatment in the instant invention without undue experimentation.

As to the protozoan parasite, the direction and guidance in the specification is notably limited to intracellular parasites that cause malarial infection such as Plasmodium species. While this is sufficient guidance and direction for inhibiting proliferation, retarding growth, and killing

Plasmodium parasites such as P. falciparum, it does not teach or suggest how to treat alternative protozoan parasites such as Trichomonas vaginalis, for example. Based on this limited disclosure and direction, one of the skill in the art would not know how to treat extracellular protozoan parasites with different life cycles and which exhibit different parasitic infectivity using knowledge taught by the instant invention without undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-6, 9-13, 15, 17-19, 22-23, and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Seguin et al. (The Journal of Experimental Medicine, 1994).

Seguin et al. teach the importance of CD8 T-cells and interferon (IFN-γ) as components in the regulation of induced nitric oxide synthase (iNOS) in liver which contribute to the protective response of mice immunized with irradiated malaria sporozoites (liver stage) of Plasmodium berghei. Specifically, Seguin et al. teach that IFN-γ, provided by CD8 T-cells, kills parasites by stimulating or inducing malaria-infected liver cells, hepatocytes, and Kupffer cells to produce nitric oxide (NO) for the destruction of hepatocytes or parasites within the cells in both mice and humans (see Abstract). Seguin et al. also teach that intraperitoneal injection of

(neutralizing) mAbs to IFN-γ during sporozoite challenge blocks the expression of iNOS mRNA and ablates protection in immunized mice causing parasitemia (see page 356, column 1). Likewise, in vivo depletion of CD8 T-cells with mAbs after immunization and before sporozoite challenge also results to parasitemia (see page 357, column 1). To further determine the participation of NO to protective response to malaria, L-arginine analogues were orally administered (gastric instillation) to immunized mice before sporozoite challenge and found that substrate inhibitors for NOS suppress NO synthesis and NO-mediated events in vivo and in vitro (see page 355, column 1). While immunity in Seguin's study is directed against liver stage malaria, another publication (Taylor-Robinson et al.), reported that induction of NO by T_h1 CD4 cells controls blood stage malaria. In conclusion, NO production is required for protection in irradiated sporozoite-immunized mice and induction of NOS in liver depends on the presence of CD8 and INF-γ.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-7, 9-13, 15, and 17-26 are rejected under 35 U.S.C. 103(a)as being unpatentable over Kremsner et al. (Transactions of the Royal Society of Tropical Medicine and Hygiene, 1996) in view of Liew et al. (Eur Immunol., 1991).

Kremsner et al. teach that high plasma levels of NO in acute phase of Plasmodium falciparum malaria predicts accelerated cure which provides evidence of the protective role of NO in malaria (see Abstract). Kremsner et al. teach that the production of NO is induced by cytokines as shown in vitro with murine macrophages, in vivo in dogs and in vitro with human cells. Kremsner et al. teach that high plasma levels of NO have previously been reported in P. falciparum and P. vivax and that NO has been shown to be toxic in vitro for P. Falciparum (see page 44). In their study, Kremsner et al. measured nitrite and nitrate, stable products of nitric oxide, in plasma of semi-immune patients and found that upon admission, NO correlated with parasitemia and was significantly higher in patients with severe malaria than in patients with uncomplicated malaria (see page 46, column 1). Alternatively, in another publication (Camerron et al.) the duration of coma in cerebral malaria has been shown to be inversely correlated with NO plasma levels which provides evidence that excessive production of NO may also be

deleterious. However, Kremsner et al. teach that NO produced within the network of a **directed immune response** plays a key protective role against malaria infection.

Kremsner et al. is silent in specifically teaching modulation of NO synthesis in NO modifying agents for purpose of treatment of parasitic infection.

Liew et al. teach that murine peritoneal macrophages which are activated with IFN-γ and IFN-α and lipopolysaccharides (LPS) produce high levels of nitric oxide and are efficient in killing intracellular protozoan parasites such as Leishmania major in vitro (see page 2490). Liew et al. further teach that macrophages treated with IL4 causes loss of response to activation with IFN-γ and IFN-α and lipopolysaccharides (LPS) in terms of NO synthesis and leishmanicidal activity (see page 2491). With that, Liew et al. suggest a regulatory pathway by which T helper type 2 (T_h2) cells modulate induction of NO synthase on macrophages via regulation of T helper type 1 (T_h1) cell function which may have a direct implication on host defense against intracellular pathogens (see page 2489, column 2). Liew et al. studied the activity of NO modulating agents and found that T_h1 cells produce IFN-γwhich activates macrophages to kill intracellular parasites through induction of NOS and T_h2 cells inhibit the action of this enzyme via IL4 that they secrete which provides a mechanism to regulate immunity to murine leishmaniasis (see page 2493).

Given the teaching that NO, in adequately effective concentrations, has known mechanisms for killing, inhibiting proliferation, and retarding growth of intracellular parasites such as Plasmodium species or Leishmania species, it would have been obvious to one of

ordinary skill in the art at the time of the invention to incorporate the teaching of Liew in modulating the effects and concentration of NO into the teaching of Kremsner in effectivity of NO in ameliorating malarial symptoms because Kremsner specifically suggested the need for a **directed immune response** to effect protective role of NO against malaria infection. One of ordinary skill in the art at the time of the invention would have been motivated to combine the teaching of Liew with the teaching of Kremsner because controlled, regulated, and directed modulation of NO whose effect is optimally limited by specific dosages, which can otherwise be potentially toxic to the system, is needed to provide acceptable treatment method of a malarial infection such as taught by the instant infection.

7. Claims 1, 8, 14, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seguin et al. or Liew et al. in view of Stamler et al. (Proc. Natl. Acad. Sci. USA, 1992).

Seguin et al. or Liew et al. have been discussed supra. Sequin et al. and Liew et al. are silent in the teaching of NO (donor) or NO modulating agent as comprising nitrosothiol.

Stamler et al. teach that nitric oxide reacts in the presence of specific protein thiols to form S-nitrosoprotein derivatives. Human plasma contains 7μm nitrosothiols of which 96% are S-nitrosoproteins, 82% of which is accounted for by nitroso-serum albumin. Stamler et al. teach that administration of monomethyl-L-arginine which is a selective and potent inhibitor for nitric oxide synthetase decreases nitrosothiol by 40%. These data suggest that naturally produced nitric oxide circulates in the plasma primarily complexed in S-nitrosothiol species (see Abstract).

Stamler et al. also specifically teach that pharmacological interventions that modulate nitric oxide generation changes plasma levels of S-nitrosothiols. The abundance of nitrosothiols in plasma compared with free nitric oxide suggests that plasma S-nitrosothiols serve as reservoir for nitric oxide to effectively buffer its concentration (see page 7677). Table 1 lists plasma levels of nitric oxide and nitrosothiols in humans.

Given the teaching that nitric oxide naturally exists in the plasma as being primarily complexed in S-nitrosothiol, it would have been obvious to one of ordinary skill in the art at the time of the invention to apply the teaching of Seguin and Kemsner of the mechanism involved in modulating NO levels for treatment of malarial infections caused by Plasmodium, so as to be applicable and effective in its state as being complexed in the nitrosothiol species.

Seguin, Liew, and Stamler are silent in teaching administration of NO by inhalation to increase systemic NO levels and NO effects. However, NO exists naturally in a gaseous state. Inhalation of gaseous pharmaceutical compounds to administer treatment is a well-known art and conventional in the field of medicine. With that teaching combined with knowledged taught by prior art, it would have been an obvious design choice to administer NO in its natural state as a pharmaceutical compound for treating malarial infections.

8. No claims are allowed.

Remarks

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Radomski et al. (Br J Clin Pharmacol, 1995) teach systemic effects of S-nitroso-glutathione in the human following intravenous infusion.

Thurring et al. (Eur J Immunol, 1995) teach that NO generated by inducible isoform of NOS is implicated in immunological processes including killing of intracellular parasites.

Gibaldi (Therapeutic Review, 1993) teaches nitric oxide and its role in human physiology and immunology.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Friday from 7:00 AM to 4:30 PM. The examiner can also be reached on alternate Fridays at 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel or Long Le, can be reached on (703) 308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

6/20/00

Gailene R. Gabel
Patent Examiner
Art Unit 1641